502.1

DISCRIMINATION LEARNING WITH INJECTIONS OF MORPHINE INTO THE PARABRACHIAL NUCLEUS, BUT NOT INTO THE VENTRAL TEGMENTAL AREA (VTA)

T.V. Jaeger* and D. van der Kooy. Dept. of Anatomy, Univ. of Toronto, Toronto, Canada M5S 1A8.

In a previous study, we demonstrated a dissociation between the neuroanatomical sites which mediate the motivational effects of morphine and its discriminative effects. Morphine was found to have both aversive and rewarding motivational effects in the VTA, but not in the parabrachial nucleus (PBN). Conversely, morphine produced discriminative effects in the PBN, but not in the VTA. To extend these studies, we use a taste aversion model of discrimination to show that 1) the discriminative effects of morphine within the PBN are specific to the activation of opiate receptors and 2) injections of morphine into the PBN, but not into the VTA, may serve as a stimulus for discrimination learning. Rats were injected with morphine (5 mg/kg, i.p.) 15 min prior to the presentation of a 0.1% saccharin solution. Lithium chloride (130 mg/kg) was injected immediately after 20 min of exposure to the flavour. On alternate days, an injection of 0.9% saline both preceded and followed the presentation of saccharin. Unilateral guide cannulae were then implanted into the PBN and generalization to central routes of administration was evaluated following the microinjection of 2.5 and 5 µg of morphine and 2.5 and 5.0 µg of (+)-morphine. Stimulus generalization was observed with 2.5 and 5.0 µg of morphine, while the inactive (+)-isomer of morphine failed to produce responses reliably different from the saline training condition.

Separate groups of rats received bilateral cannulae implants into either the PBN or the VTA and were trained in the discrimination task using either 2.5 or 5.0 µg of intracerebral morphine as the training stimulus. Rats with implants into the VTA did not demonstrate differential responding under either dose of morphine tested. Rats with implants in the PBN, however, quickly learned the task, consuming significantly less saccharin after morphine than after saline injections. The data demonstrate that injections of morphine into the PBN are *sufficient* to support discrimination learning.

502.2

AVERSIVE EFFECTS OF THE SYNTHE
RATS

I. S. McGregor* and C. Issakid
Sydney, NSW, 2006, Australia.

Despite the widespread use
addictive potential of this drug
scientifically and politically.
potent synthetic cannabin
of research into canna
hedonic properties of C
initial experiment showed th
locomotor activity, indicating b
(100 µg/kg) caused a sedative
conditioned place preference para
powerful aversion to an environment in
µg/kg). A lower dose (10 µg/kg) produced
experiment using the conditioned taste aversion
rats developed a strong aversion to a fluid (saccha
prior to administration of 100 µg/kg CP 55,940. In a
shown that rats under the influence of CP 55,940 (10 or 1
a higher rate of anxiety-related ultrasonic vocalisation in an
which they had previously received mild footshock. This sug
aversive effects of CP 55,940 summated with the aversive effe
environment to magnify anxiety. It is concluded that CP 55,940 is ave
rats, probably due to an anxiogenic effect. The utility of animal models
increasing understanding of human cannabis use is therefore open
question.

502.3

FUNCTIONAL MAGNETIC RESONANCE IMAGING OF NICOTINE EFFECTS ON BRAIN ACTIVATION BY A VISUAL SPATIAL WORKING MEMORY TASK IN HUMANS.

E.A. Stein*, A.S. Bloom, J. Pankiewicz, J-K. Cho, S.A. Fuller, D.C. Osmon+, Y. Suchy+, and J.R. Zigun. Medical College of Wisconsin and University of Wisconsin+, Milwaukee, WI 53226.

Nicotine facilitates human attention, memory and sensorimotor function. A visual spatial working memory (VSWM) task that utilizes these functions activates several frontal and parietal cortical regions as measured by functional magnetic resonance imaging (FMRI). Since evidence exists for the involvement of forebrain dopamine (DA) systems in VSWM as well as the effects of nicotine on DA systems, we examined the effects of nicotine on task-induced FMRI activation. Single shot echo planar imaging was obtained on a 1.5 Tesla GE Signa scanner using an insertable, balanced torque, 3-axis head gradient coil designed for rapid gradient switching. To obtain images throughout the entire brain volume, a shielded quadrature elliptical endcapped transmit/receive birdcage radio frequency coil was used. Four experienced smokers performed the VSWM task while FMR data were acquired (TR=5 sec; TE=40 msec; 8 mm slice thickness). A trial consisted of 7 cycles of task repetition (30 sec rest, 45 sec task). Nicotine (0.75, 1.5 or 3.0 mg) or saline was injected iv over a 15 sec period after the third task cycle. The most common nicotine effect observed (defined as appearing in 4 contiguous pixels) was an increase in the magnitude of the task-induced activation response in both frontal and parietal regions with doses as low as 0.75 mg. In each case, an increase in activation magnitude was seen within 1 minute of drug (but not saline) administration. The average injection-induced increase in signal was 5.3% after saline, 53.5% after the low (0.75 mg) nicotine dose, and 86.3% after the medium (1.5 mg) nicotine injection. The present data suggest that nicotine enhances regional neuronal activation induced when performing a VSWM task.

502.4

MICRODIALYSIS ASSESEMENT OF NUCLEUS ACCUMBENS GLUTAMATE DURING IV HEROIN SELF-ADMINISTRATION

K. Bonter,*[1,2] K. Leeb,[1,3] D. Pocock,[1,2] R. A. Wise,[1,3] Ctr Stud Behav Neurobiol[1] and Depts Chem Biochem[2] and Psychol,[3] Concordia Univ., Montréal, Que, CANADA H3G 1M8

Nucleus accumbens septi (NAS) is identified as a critical structure for the habit-forming actions of opiates, and glutamatergic afferents from the frontal cortex have been suggested to regulate NAS activity. Accordingly, the present study was designed to determine fluctuations in NAS glutamate levels during intravenous heroin self-administration. Rats with NAS dialysis probes were allowed to self-administer heroin. Extracellular fluid from NAS was sampled at 4min intervals by micro-dialysis and glutamate was assayed using HPLC with electrochemical detection of OPA amino acid derivatives. Glutamate concentrations in the dialysate increased during heroin self-administration stabilizing at 200% to 400% above baseline. Glutamate concentrations appeared to increase further during extinction conditions that followed the self-administration period. The glutamate elevation during self-administration coincides with reported elevations in dopamine; the elevation in glutamate during extintion occurs at a time when dopamine levels are falling. Thus behavioral states appear capable of dissociating fluctuations in extracellular levels of the two transmitters, suggesting a more complex glutamate-dopamine interaction than has been recently hypothesized.

502.5

IBOGAINE ANTAGONISM OF MORPHINE-INDUCED HYPERACTIVITY: ENHANCEMENT BY PRIOR MORPHINE EXPOSURE AND ROLE OF KAPPA OPIOID RECEPTORS.

S.M. Keefner* and S.D. Glick. Dept of Pharmacology and Toxicology, Albany Medical College, Albany, NY 12208

Ibogaine, an indole alkaloid, is currently being investigated as a potential anti-addictive therapy. It has been shown to decrease morphine self-administration and to inhibit both morphine-induced locomotor stimulation and morphine-induced dopamine release in the nucleus accumbens and striatum of rats. However, in both rats and humans, the effects of ibogaine appear to be quite variable; the present study sought to determine if prior morphine history might account for individual differences in sensitivity to ibogaine. Female Sprague-Dawley rats, pretreated for 2 days with morphine (30 mg/kg, i.p.) before receiving ibogaine (40 mg/kg, i.p.), showed significantly less locomotor activity in response to morphine (2.5-30 mg/kg, i.p.) than controls pretreated with saline prior to ibogaine. Thus, prior morphine exposure enhanced ibogaine antagonism of morphine-induced locomotor activity. To study whether ibogaine's effects may be related to activation of the kappa opioid receptor, for which ibogaine has affinity, two kappa agonists were administered using the same treatment parameters. The selective kappa agonists, U50488 (10 mg/kg, i.p.) and U62066 (1 mg/kg, i.p.), when administered in place of ibogaine, mimicked ibogaine's effects. Furthermore, in preliminary studies, the selective kappa antagonist nor-binaltorphimine (10 mg/kg, s.c.) appeared to reverse the ibogaine-induced antagonism of morphine. These results suggest that the long-lasting effects of ibogaine may be due to persisting levels of ibogaine and/or an ibogaine metabolite interacting at kappa opioid receptors to yield anti-addictive effects. (Supported by DA03817)

502.6

HEROIN SELF-ADMINISTRATION PRODUCES BIOCHEMICAL ADAPTATIONS SIMILAR TO CHRONIC MORPHINE TREATMENT IN BRAIN REWARD REGIONS.

A.W. McClenahan, D.W. Self, D. Beitner-Johnson, R.Z. Terwilliger, and E.J. Nestler* Dept of Pharmacology and Psychiatry, Yale Univ. Sch. of Med., New Haven, CT 06508

The mesolimbic dopamine system, specifically the ventral tegmental area (VTA) and its projection to target neurons in the nucleus accumbens (NAc), mediates some of the reinforcing effects of drugs of abuse. Previous results from rats forcibly treated with chronic morphine found several biochemical adaptations in the VTA and NAc (see Neuron 11:995, 1993). This experiment validates the previous findings by using the animal model of drug self-administration (SA), which better approximates human drug addiction. In these studies, rats self-administered heroin in limited, daily 6-hr test sessions for three weeks. A yoked-heroin and a yoked-saline control group were used for comparison. The findings show that opiate SA produces similar biochemical adaptations, when compared to animals receiving yoked injections of saline, as produced by chronic, forced opiate treatments. These include an increase in tyrosine hydroxylase (TH) and glial fibrillary acidic protein, and a trend toward a decrease in neurofilaments, in the VTA, and an increase in cAMP-dependent protein kinase activity and a trend toward a decrease in Gi proteins, in the NAc. Interestingly, heroin SA produces one important adaptation in the NAc, a decrease in TH levels, not seen in animals treated chronically with morphine. There were no differences between heroin SA rats and rats receiving yoked heroin injections.

Although the heroin self-administering rats failed to show signs of physical dependence, biochemical adaptations in the mesolimbic dopamine system of these rats suggest that these changes could contribute to the motivational aspects of drug addiction.